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Thrombotic Complications in Essential Thrombocythemia With Relatively Low Platelet Counts

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Essential thrombocythemia (ET) is often associated with thrombotic and hemorrhagic complications, mostly at platelet counts exceeding 600 × 10^9/L. There are, however, a few reports of such complications in ET at considerably lower platelet levels and the therapeutic approach to affected patients with relatively low platelet counts is still controversial. In the present study, the first to directly address the issue of hemostatic manifestations at relatively low platelet counts, we have determined the lowest platelet counts associated with such manifestations in 56 consecutive ET patients. Clinical manifestations related to ET were recorded in 46 (82%) patients. Of the symptomatic patients, 32 (70%) had symptoms at platelet counts lower than 600 × 10^9/L, 23 (50%) at counts lower than 500 × 10^9/L, 10 (22%) at counts lower than 400 × 10^9/L, and 6 patients (13%) at platelet counts as low as 300–350 × 10^9/L. Severe complications occurred at platelet counts lower than 600 × 10^9/L in 10 patients (22%), lower than 500 × 10^9/L in 7 (15%), and at lower than 400 × 10^9/L in 2 (4%). Thrombotic neurologic symptoms were the most common (31 patients, 67%), followed by peripheral vascular symptoms (17 patients, 37%); hemorrhagic complications were relatively rare (3 patients, 7%). In most cases, cessation or improvement of clinical manifestations was observed only after further reduction in platelet counts. In conclusion, thrombotic manifestations, including severe ones, are not uncommon in ET at relatively low platelet counts. We recommend that symptomatic patients with relatively low platelet counts be treated and the platelet counts further reduced well into the lower normal range. Am. J. Hematol. 56:168–172, 1997.

Key words: essential thrombocythemia; thrombotic complications; platelet counts

INTRODUCTION

Essential thrombocythemia (ET) is a chronic myeloproliferative disorder characterized by the elevation of platelet count, which results from the clonal proliferation of a single neoplastic multipotent stem cell, affecting primarily megakaryocyte production [1,2]. ET was first described in 1934 [3], but firm guidelines for its diagnosis were established only in 1982 by the Polycythemia Vera Study Group [4]. ET is often associated with hemostatic complications, both thrombotic and hemorrhagic [5,6], with an incidence of thrombosis at presentation as high as 84% [7]. These complications, most often thrombotic, are more common in patients with high platelet counts, but no clear correlation between the degree of thrombocythemia and the risk of complications has been shown [8–10]. On the other hand, it was demonstrated that lowering the platelet count had abrogated the clinical manifestations and improved platelet function in vitro [11–13]. The importance of lowering the platelet count in symptomatic patients is now well established [11,14,15]. It is also generally agreed that asymptomatic patients with very high platelet count should be treated with platelet-reducing agents in order to prevent complications [16]. The management of patients with mild to moderate thrombocythemia is still controversial. There are reports of thrombotic manifestations at relatively low platelet counts (<600 × 10^9/L) and occasion-

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ally at counts within normal limits (during platelet-lowering treatment) [12,17,18]. However, the incidence of hemostatic complications in ET patients with relatively low platelet count has not been studied directly. In the present study we have determined the lowest platelet counts that were associated with thrombotic and hemorrhagic manifestations in such patients.

PATIENTS AND METHODS

Between the years 1976–1992, 56 ET patients were diagnosed, followed, and treated at the Institute of Hematology. The diagnosis of ET was established according to the criteria of the Polycythemia Vera Study Group [4,6]. Platelet counts were determined automatically by Coulter (Hialeah, FL) S^+ and Technicon (Tarrytown, NY) H1 counters. No known cause for reactive thrombocytosis had been found in a comprehensive evaluation. Iron stores were assessed by serum iron, transferrin, and ferritin levels and by bone marrow iron stain. Of the 39 patients with hemoglobin levels >13.0 g/dL, the red cell mass was determined in 29, and was found to be normal in each case. Only in 4 cases of hemoglobin levels >14.0 g/dL the red cell mass was not evaluated. Bone marrow examination was performed in 51 patients. Fibrosis constituted less than one-third of marrow cellularity in all cases. All patients were negative for the Philadelphia chromosome on G-banding cytogenetic analysis performed according to standard methods. Each medical file was reviewed for thrombotic and hemorrhagic manifestations, for the lowest platelet counts recorded in association with these manifestations and for the consequences of further reducing the platelet counts. Platelet counts $<600 \times 10^9$/L, during follow-up, were considered relatively low. Minor manifestations were defined as headache, tinnitus, dizziness, paresthesias, erythromelalgia, leg pain, digital cyanosis, ecchymosis, gingival bleeding, and epistaxis. Severe complications were defined as cerebrovascular accident (CVA), transient ischemic attack (TIA), deep venous thrombosis, visual disturbances, and digital gangrene. Hemostatic evaluation included determination of bleeding time, measured by the Ivy method, spontaneous platelet aggregation, and aggregation in response to epinephrine, adenosine diphosphate (ADP), and collagen, measured by Biodata (Hatboro, PA) 4-channel aggregometer.

RESULTS

Patients and Laboratory Characteristics

The median age at the time of ET diagnosis was 66 years (range 28 to 86 years); 6 patients (10.7%) were younger than 40 years. The M:F ratio was 1:1.24. Platelet counts at the time of diagnosis were 600×10^9/L–$1{,}920 \times 10^9$/L (median, $1{,}125 \times 10^9$/L). The peripheral blood counts at presentation are shown in Table I. The median duration of follow-up was 45 months (range 3–172 months). Platelet aggregation was tested in 46 patients and, as shown in Table I, loss of responsiveness to epinephrine was the most common abnormality. Prolonged bleeding time was uncommon.

TABLE I. Summary of Peripheral Blood Counts at Presentation (56 Patients), Platelet Function Tests (46 Patients), and Bleeding Time (49 Patients) in Essential Thrombocythemia

Laboratory findings	No. of patients (%)
Hemoglobin level	
<13.0 g/dL	17 (30.4)
13.0–15.0 g/dL	29 (51.8)
>15.0 g/dL	10 (17.8)
Leukocyte count	
$<8.0 \times 10^9$/L	15 (26.8)
$8.0–11.9 \times 10^9$/L	25 (44.6)
$12.0–16.0 \times 10^9$/L	12 (21.4)
$>16.0 \times 10^9$/L	4 (7.2)
Platelet count	
$<1{,}000 \times 10^9$/L	31 (55.4)
$1{,}000–1{,}500 \times 10^9$/L	19 (33.9)
$>1{,}500 \times 10^9$/L	6 (10.7)
Abnormal platelet aggregation	
In response to epinephrine	35/46 (76.1)
In response to ADP	26/46 (56.5)
In response to collagen	25/46 (54.3)
Spontaneous aggregation	13/46 (28.3)
Prolonged bleeding time	2/49 (4.1)

Clinical Manifestations and Platelet Counts

Clinical manifestations related to thrombocythemia were recorded in 46 patients (82%). As shown in Table II, 31 of the 46 symptomatic patients (67%) had 47 neurologic manifestations and 17 (37%) patients had 22 peripheral vascular thrombotic manifestations. Only 3 patients (7%) had 4 hemorrhagic complications, which occurred at platelet counts of 500×10^9/L–645×10^9/L. Severe manifestations occurred at platelet counts lower than 600×10^9/L in 10 patients (22%), lower than 500×10^9/L in 7 (15%), and lower than 400×10^9/L in 2 (4%). The spectrum and distribution of symptoms among the patients with platelet counts lower than 600×10^9/L were similar to that among all symptomatic patients (Table II). We have not found any association between platelet counts and type of symptoms. Neither was any correlation found between type of aggregation abnormalities and clinical symptoms. The lowest platelet counts recorded in association with symptoms ranged from 300×10^9/L to $1{,}000 \times 10^9$/L (median, 463×10^9/L). Among the 46 symptomatic patients, manifestations were recorded at platelet counts lower than 600×10^9/L in 32 (70%), at lower than 500×10^9/L in 23 (50%), and at lower than 400×10^9/L in 10 (22%) patients. In 6 patients (13%) symptoms were recorded at platelet counts as low

TABLE II. Summary of Hemostatic (Thrombotic and Hemorrhagic) Manifestations in Essential Thrombocythemia of All Symptomatic Patients and Those With Relatively Low Platelet Counts (<600 × 10^9/L)*

Hemostatic manifestation	All symptomatic patients [N = 46 (%)]	Platelets <600 × 10^9/L symptomatic patients [N = 32 (%)]
Thrombotic-neurologic	**31 patients (67.4)**	**20 patients (62.5)**
Dizziness	16 (34.8)	12 (37.5)
Paresthesias	10 (21.7)	6 (18.8)
Headache	8 (17.4)	7 (21.9)
Visual disturbances	6 (13.0)	5 (15.6)
TIA/CVA	5 (10.9)	3 (9.4)
Tinnitus	2 (4.3)	1 (3.1)
Thrombotic-peripheral-vascular	**17 patients (37.0)**	**13 patients (40.6)**
Digital ischemia	10 (21.7)	7 (21.9)
Erythromelalgia	5 (10.9)	3 (9.4)
Leg pain	5 (10.9)	4 (12.5)
Venous thrombosis	2 (4.3)	0
Hemorrhagic	**3 patients (6.5)**	**2 patients (6.3)**
Ecchymosis	2 (4.3)	1 (3.1)
Gingival bleeding	1 (2.2)	1 (3.1)
Epistaxis	1 (2.2)	0

*TIA = transient ischemic attack; CVA = cerebrovascular accident.

as 300 × 10^9/L–350 × 10^9/L. These figures represent 56, 41, 18, and 11%, respectively, of all patients (56) in the study. Only ten patients (18%) were asymptomatic at presentation and during follow-up.

Fifty-two patients were treated with platelet-reducing agents (44 with hydroxyurea and 8 with busulfan) and 47 patients were treated with antiplatelet agents (41 with aspirin combined with/without dipyridamole and 6 with dipyridamole alone) throughout the follow-up period. Most of the patients were treated continuously, and dosage of platelet-reducing agents (sometimes only minimal dose) was adjusted according to peripheral blood counts performed periodically. Of the 10 asymptomatic patients, 7 were treated with aspirin and 8 were treated with hydroxyurea (because of high platelet counts). Of the 46 symptomatic patients, 43 were already treated with platelet-reducing agents and 36 with antiplatelet agents when manifestations were recorded. Consequently, treatment with hydroxyurea was started in 1 patient, dosage of hydroxyurea was increased in 22 patients, aspirin was added in 4 patients, and treatment was not changed in 19 patients. Subsequently, cessation or significant amelioration of manifestations was observed and/or reported by 42 (91%) patients, and platelet counts ranged from 162 × 10^9/L to 760 × 10^9/L (median, 356 × 10^9/L). The decrease in platelet counts ranged from 60 × 10^9/L to 460 × 10^9/L (median, 145 × 10^9/L) (Fig. 1). In 4 patients (2 with CVA, 1 with arterial thrombosis, and 1 with venous thrombosis) complications were permanent.

DISCUSSION

Hemostatic complications in ET at platelet counts lower than 550 × 10^9/L to 600 × 10^9/L are considered to be infrequent [9,18–20]. However, several such cases have been described. Hehlmann et al. [7], in a series of 61 ET patients, found 6 cases of thrombotic complications at platelet counts lower than 600 × 10^9/L; of these, 3 were lower than 400 × 10^9/L. Cortelazzo et al. [21], in a series of 114 patients, had one with thrombosis at a platelet count as low as 490 × 10^9/L. Korenman [17] reported a symptomatic case at a platelet count of 224 × 10^9/L. In a series of 173 patients, Fenaux et al. [22] noted that few patients had symptoms as long as their platelet counts were higher than 450 × 10^9/L–500 × 10^9/L. Jabaily et al. [12] described 3 patients with platelet counts less than 350 × 10^9/L, one with 414 × 10^9/L, and one with 494 × 10^9/L who had neurologic manifestations.

In our study we have directly addressed the issue of hemostatic manifestations among ET patients with relatively low platelet counts. Of the 46 symptomatic patients, hemostatic complications, thrombotic in almost all cases, were observed in 32 (70%) at platelet counts lower than 600 × 10^9/L, in 23 (50%) at platelet counts lower than 500 × 10^9/L, and in 10 (22%) at platelet counts lower than 400 × 10^9/L. Likewise, we found that severe complications occurred at platelet counts lower than 600 × 10^9/L in 10 (22%) patients, lower than 500 × 10^9/L in 7 (15%), and lower than 400 × 10^9/L in 2 (4%). In contrast with the aforementioned, it is generally agreed that reactive thrombocytosis (RT) is not associated with increased risk for thrombotic and hemorrhagic complications even at high platelet counts [15,23,24] and, therefore, we have not included such a control group in our study.

It is widely recognized [6,7,12,21,25–27] that the most common hemostatic complications in ET are neurologic-

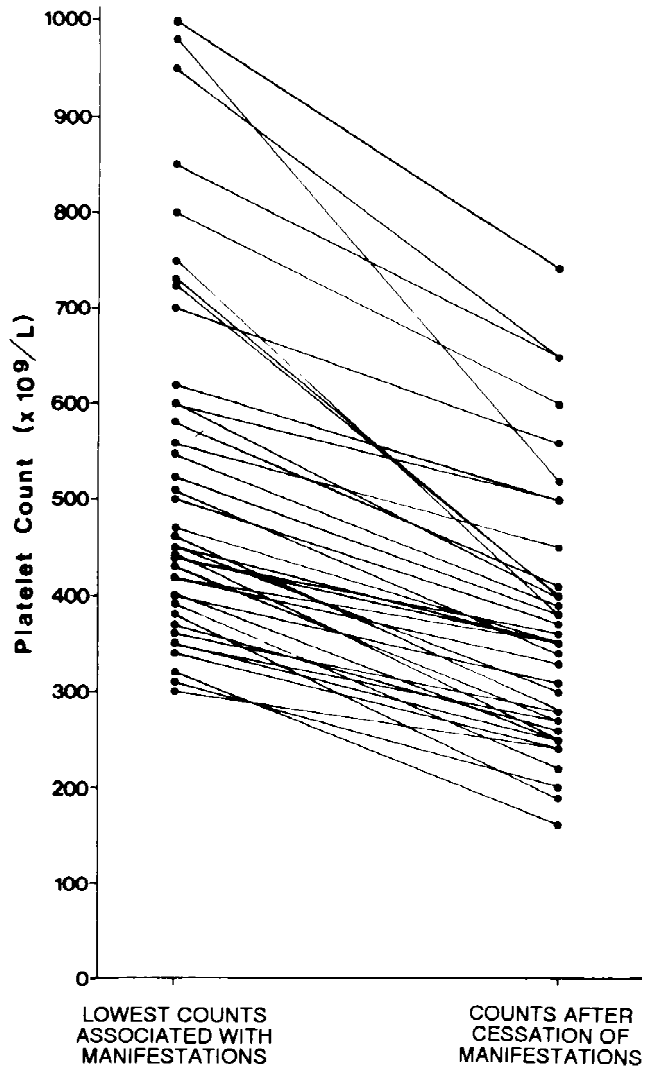

Fig. 1. Changes in platelet counts, from the lowest counts recorded while patients were symptomatic to counts recorded on resolution of symptoms, in 42 ET patients (4 patients with permanent complications are not included).

thrombotic while symptoms related to peripheral vascular thrombotic complications are less frequent and hemorrhagic manifestations are relatively rare. Similar findings were recorded in our series. The relative frequency of the clinical manifestations among those patients who had platelet counts lower than 600×10^9/L was similar to that among all symptomatic patients (Table II).

The most characteristic aggregation abnormality in ET is loss of responsiveness to epinephrine, followed by abnormal responses to ADP and collagen. The prevalence of aggregation abnormalities in our series was similar to that in others [5,7,9,18,21,22]. Forty-three (93%) of the 46 symptomatic patients were already treated with platelet-reducing agent and 36 (78%) with antiplatelet agents when complications occurred. In most cases, the cessation or improvement of symptoms was achieved only after further reduction in platelet counts, regardless of antiplatelet treatment. These findings were also observed in patients with relatively low platelet counts.

The therapeutic approach to ET patients with relatively low platelet counts is controversial. Schafer [23], Meisel et al. [27], and others [8,26] have recommended that only patients who are symptomatic or at high risk for cardiovascular complications should be treated. Cortelazzo et al. [9,21] and Jabaily et al. [12] have suggested that platelet counts be kept at a level lower than 600×10^9/L as long as possible. Mitus and Schafer [15] as well as Tefferi and Hoagland [20] have recommended controlling the platelet counts of symptomatic ET patients at less than 500×10^9/L. Moreover, Pearson [28], Case [11], and several others [6,22,25] have suggested lowering the platelet count to within the normal range. The results of our study strongly support the more aggressive approach.

CONCLUSIONS

In the present study we have demonstrated that thrombotic manifestations, including severe complications, are not uncommon in ET patients at relatively low platelet counts, and may occur more frequently than has been previously suggested. We also have found that, in most cases, cessation or improvement of symptoms was observed only after further reduction in platelet counts. Based on our data we conclude that symptomatic ET patients with relatively low platelet counts should be treated and the platelet counts further reduced well into lower normal range. The effect of a more aggressive approach in reducing the incidence of thrombotic complications in ET patients with low platelet counts merits further investigation.

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